Remarks/Arguments:

Claim 11 is canceled without prejudice. Claims 1 and 5-7 are amended. Claims 34-35 are added. Support for the amendment and the new claims can be found, e.g., at page 4, lines 17-20; page 5, line 30 – page 6, line 2; page 11, lines 13-15; page 16, line 32 – page 17, line 7; page 23, line 20 – page 24, line 11; and page 25, line 10 – page 30, line 17, as well as Koyanagi et al. (2005) J. Clin. Oncol. 23(31):8057-64 ("Koyanagi") and the declaration submitted herewith by Dr. Hoon, one of the inventors. No new matter is introduced.

Claims 1-7, 10, and 31-35 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

New Rejections Based on Amendments

CLAIM REJECTIONS UNDER 35 USC § 112, SECOND PARAGRAPH

Claims 1-7 and 10-11 stand rejected as being indefinite on two grounds:

(1) The Examiner stated that claims 1-7 and 10-11 are incomplete because "the claims do not indicate what kind of levels correlate with melanoma recurrence, disease-free survival, or overall survival." Without acquiescence to the Examiner's position, Applicants have amended claim 1 by adding a limitation "wherein, as compared to control levels, an increase in the levels of the nucleic acid targets is indicative of an increase in melanoma recurrence, a decrease in disease-free survival, or a decrease in overall survival, and a decrease in the levels of the nucleic acid targets is indicative of a decrease in melanoma recurrence, an increase in disease-free survival, or an increase in overall survival." This limitation clearly indicates the relationship between the levels of the nucleic acid targets and melanoma recurrence, disease-free survival, and overall survival.

(2) The Examiner stated that "[i]t is not clear from the claims or the specification what biological samples are 'associated with' melanoma" and that "one of ordinary skill in the art would not be reasonably apprised of the scope of the

invention." Although Applicants disagree, to expedite the prosecution of the application, Applicants have deleted the limitation "wherein the biological sample is associated with melanoma" from claim 1.

In light of the foregoing, Applicants respectfully submit that the rejections have been overcome and should be withdrawn.

CLAIM REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH - ENABLEMENT

Claims 1-7 and 10-11 stand rejected for lack of enablement on two grounds:

(1) The Examiner stated that:

> ...the specification, while being enabling for a method for melanoma prognosis comprising isolating nucleic acid from sentinel lymph node samples and blood samples obtained from a melanoma patient and amplifying nucleic acid targets comprising GalNacT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein an increase in expression of said targets, as compared to expression of said targets in corresponding normal lymph tissue or normal blood samples, is indicative of an increase in metastatic melanoma recurrence, a decrease in metastatic-melanoma free survival, and a decrease in patient survival, does not reasonably provide enablement for a method for melanoma prognosis comprising isolating nucleic acid from just *any* biological sample from a melanoma patient deemed "associated with melanoma" and amplifying nucleic acid targets comprising GalNacT, PAX3, MART-1, MAGE-A3, and tyrosinase, wherein *any* level of said targets is indicative of melanoma recurrence, survival without any kind of disease, and overall survival.

Applicants respectfully disagree. However, for the sole purpose of moving this application forward, Applicants have amended claim 1 such that it now recites "a sentinel lymph node (SLN) sample" and "wherein, as compared to control levels, an increase in the levels of the nucleic acid targets is indicative of an increase in melanoma recurrence, a decrease in disease-free survival, or a decrease in overall survival, and a decrease in the levels of the nucleic acid targets is indicative of a

decrease in melanoma recurrence, an increase in disease-free survival, or an increase in overall survival." This amendment overcomes the rejection.

(2) The Examiner further stated that "the specification provides no guidance, working examples, or exemplification demonstrating how detecting the expression of the target genes in a sample could be used to 'select' any particular treatment regime from those commonly used to treat any metastatic melanoma." While not conceding the Examiner's assertion, Applicants have canceled claim 11, rending this rejection moot.

In light of the foregoing, Applicants respectfully submit that the rejections have been overcome and should be withdrawn.

CLAIM REJECTIONS UNDER 35 USC § 103(a)

Claims 31-33 stand rejected as being unpatentable over Palmieri et al. (Journal of Clinical Oncology 19(5):1437-43; "Palmieri") in view of Scholl et al. (Cancer Research 61:823-6; "Scholl") and Kuo et al. (Clinical Cancer Research 4:411-8; "Kuo"). Applicants respectfully traverse.

Claim 31 is directed to a method for detecting the expression of a panel of marker genes in a patient. The method comprises:

(a) obtaining a sentinel lymph node (SLN) sample from a melanoma patient, wherein the sample is histopathologically negative for melanoma cells;

(b) isolating nucleic acid from the sample;

(c) amplifying nucleic acid targets from a panel of marker genes, wherein the panel comprises GalNAcT, PAX3, or both; and

(d) detecting the levels of the nucleic acid targets.

Palmieri discloses detection of a combination of Tyrosinase and MART-1 markers in histopathologically negative SLN and peripheral-blood (PB) samples obtained from melanoma patients (see, e.g., page 1437, left column, 1st paragraph, lines 7-12 and 2nd paragraph, lines 3-5). Scholl discloses detection of PAX3 marker

in cultured primary melanomas and their corresponding tissue sections (see, e.g., page 823, left column, Abstract, lines 5-11 and right column, last paragraph, lines 4-6). Kuo discloses detection of GalNAcT in melanoma cell lines, primary melanoma biopsies, histopathologically positive tumor-draining lymph node (TDLN) metastases, distal organ metastases, and blood (see, e.g., page 413, right column, Table 1 and 1st paragraph following Table 1, lines 14-15; page 414, left column, Table 2).

Although Palmieri indicates that the RT-PCT assay shows good sensitivity for Tyrosinase and MART-1 markers in histopathologically negative SLN samples, it does not teach that every marker would be detectable by an RT-PCR assay in histopathologically negative SLN samples. Neither Scholl nor Kuo indicates that PAX3 or GalNacT would be detectable by an RT-PCR assay in histopathologically negative SLN samples. It is well known in the art that each gene has a unique expression pattern. The timing, location, and level of expression varies from gene to gene. Given the high unpredictability, even if one skilled in the art would have been motivated to combine Palmieri with Scholl and Kuo, there would have been no reasonable expectation of success in detecting PAX3 or GalNacT by an RT-PCR assay in histopathologically negative SLN samples, because for example the level of PAX3 or GalNacT might have been too low to be detected by RT-PCR due to either low expression of the gene or dilution of the marker by other mRNAs.

Furthermore, claim 31 is non-obvious over the cited art because the method of claim 31 has unexpected advantages. More specifically, it is the discovery of the present invention that the expression levels of a panel of marker genes including GalNAcT or PAX3 are indicative of melanoma recurrence, disease-free survival, or overall survival (see, e.g., page 25, line 10 – page 30, line 17 of the specification). Without such knowledge, one skilled in the art would not have been motivated to combine Palmieri with Kuo and Scholl to come up with the method of claim 31.

Therefore, claim 31 is patentable over the cited art. Claims 32-33, dependant directly or indirectly from claim 31, are also patentable over the cited art for at least the same reasons. The rejections should be withdrawn.

CLAIM REJECTIONS UNDER 35 USC § 112, FIRST PARAGRAPH – NEW MATTER

Claims 1-4, 6-7, and 10-11 stand rejected for reciting "wherein the biological sample is associated with melanoma" in claim 1. As mentioned above, Applicants have deleted this limitation from claim 1, rendering the rejection moot. Therefore, Applicants respectfully request that the rejection be withdrawn.

NEW CLAIMS 34-35

New claims 34-35 are identical to amended claim 1 except that a blood sample is used in the method of claim 34 and a non-sentinel lymph node (NSLN) sample is used in the method of claim 35. As mentioned above, these claims are fully supported by the specification, Koyanagi, and the declaration submitted herewith by Dr. Hoon, one of the inventors.

CONCLUSION

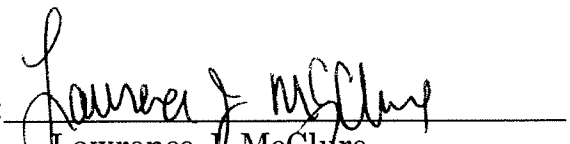
In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned at the Los Angeles, California telephone number (310) 785-4600 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Dated: December 15, 2006

By: 
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